Formation and Hydrolysis of a Diaqua(ethane-1,2-diamine)palladium(II) Complex of Ethyl Glycinate

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The reaction of $[Pd(en)(OH_2)_2]^{2+}$ (en = ethane-1,2-diamine) with ethyl glycinate has been studied by potentiometric titrations. Reaction in solution is given by equilibrium (i), where L = $H_2NCH_2CO_2C_2H_5$;

$$[Pd(en)(OH_2)_2]^{2+} + L \overset{K_1}{\rightleftharpoons} [Pd(en)L]^{2+} + 2\,H_2O \quad (i)$$

$\log K_1 = 7.12 \pm 0.03$ at 25 °C and 0.5 mol dm^{-3} KNO_3. The rate of hydrolysis of $[Pd(en)L]^{2+}$ was studied on a pH-stat. Equations (ii) and (iii) account for the kinetic data. The rate constants k_1 and k'_2

$$[Pd(en)L]^{2+} + OH^- \overset{k_1}{\rightleftharpoons} \text{product} \quad (ii)$$

$$[Pd(en)L]^{2+} + H_2O \overset{k_2}{\rightleftharpoons} \text{product} \quad (iii)$$

are 1.06×10^4 dm^3 mol^{-1} and 2.10×10^{-4} s^{-1} respectively at 25 °C and 0.5 mol dm^{-3} KNO_3, where $k'_2 = k_2[H_2O]$.

Transition-metal ions as well as a number of their complexes are known to promote the hydrolysis of esters of α-amino acids. Fairly extensive studies have been carried out on such systems by different workers with the hope that the elucidations of the mechanisms of the reactions may lead to a better understanding of the role of metal ions in enzymatic reactions.[1] Hitherto, almost all the systems investigated involved metal ions from the first-row transition elements with Cu^{II}, Ni^{II}, and Co^{III} receiving most of the attention. Little has been done on systems involving heavier transition-metal ions, although Angelici and Leach [2] have reported the hydrolysis of ethyl glycinate-*NN*-diacetic acid catalysed by Sm^{III}.

In recent articles I have pointed out that $[Pd(en)(OH_2)_2]^{2+}$ (en = ethane-1,2-diamine) can form very stable complexes with α-amino acids and peptides and can also promote the deprotonation of amide groups in some of these complexes.[3-5] In this respect the behaviour of $[Pd(en)(OH_2)_2]^{2+}$ is reminiscent of those shown by Cu^{II}, Ni^{II}, and Co^{III} except that the effect is much more pronounced in the palladium case.

The catalytic action of $[Pd(en)(OH_2)_2]^{2+}$ has also been investigated previously. Hartley and co-workers [6] reported that $[Pd(en)(OH_2)_2]^{2+}$ catalysed the nucleophilic attack of hydroxide ions on olefins. They also found that olefins were oxidised much more rapidly in the presence of $[Pd(en)(OH_2)_2]^{2+}$ than $[Pd(dien)(OH_2)]^{2+}$ (dien = diethylenetriamine) even though the two species have the same charges. On the other hand Lim and Martin [7] found that the hydrolysis of *p*-nitrophenyl acetate is catalysed by $[Pd(dien)(OH_2)]^{2+}$ but not by $[Pd(en)(OH_2)_2]^{2+}$. Thus the catalytic action of $[Pd(en)(OH_2)_2]^{2+}$ appears to depend very much on the nature of the substrates. It is of interest therefore to investigate the reactions of $[Pd(en)(OH_2)_2]^{2+}$ with esters of α-amino acids.

The results of a potentiometric titration study of the formation of the complex of $[Pd(en)(OH_2)_2]^{2+}$ with ethyl glycinate together with a pH-stat study of its hydrolysis are presented in this paper.

Experimental

Materials.—Crystalline $[Pd(en)Cl_2]$ and the solution of $[Pd(en)(OH_2)_2][NO_3]_2$ derived therefrom were prepared as reported previously.[7,8] Ethyl glycinate hydrochloride was prepared according to a literature method.[9] For reactions with $[Pd(en)(OH_2)_2]^{2+}$ the ethyl glycinate hydrochloride was converted to the nitrate by stirring it with one equivalent of $AgNO_3$, filtering, and the filtrate made up to the desired volume in a standard flask. Potentiometric titration with NaOH of a sample of the hydrochloride and a solution of the nitrate prepared from it and left standing for several hours showed that the two titration curves were superimposable. Furthermore the e.m.f. readings during titrations were very steady throughout the titrations in both cases showing that hydrolysis was very slow. Nevertheless, only freshly prepared ester solutions were used for this study in order to minimise possible error due to hydrolysis of stock solutions. Other chemicals used were of AnalaR quality.

Potentiometric Titrations.—(*a*) $[Pd(en)(OH_2)_2]^{2+}$ + *ethyl glycinate.* Potentiometric titrations were carried out on solutions containing a 1 : 1 mol ratio of $[Pd(en)(OH_2)_2][NO_3]_2$ and ethyl glycinate hydronitrate with standard NaOH solution at 25 °C and 0.5 mol dm^{-3} KNO_3 ionic strength medium. The titrations were carried out fairly rapidly since the e.m.f. readings indicate that hydrolysis of the complex occurs even at fairly low pH values. The apparatus and procedure have been described previously.[3]

(*b*) *Free ligand.* The pK_A of the ethyl glycinate was determined at the same temperature and ionic strength medium by titrating both a weighed sample of the hydrochloride and a solution of the hydronitrate derived therefrom with standard NaOH solution.

Kinetic Measurements.—The rate of hydrolysis of the $[Pd(en)(OH_2)_2]^{2+}$ complex of ethyl glycinate was followed on a Radiometer TTT2 Titrator and SBR2 Titrigraph used as a pH-stat. In a typical experiment $[Pd(en)(OH_2)_2][NO_3]_2$ (10 cm^3, 2.000×10^{-2} mol dm^{-3}), KNO_3 (50 cm^3, 1.000 mol dm^{-3}), and water (30 cm^3) were placed in a jacketed glass vessel maintained at a constant temperature by circulating water from a constant temperature bath (Haake type NR22). A glass electrode (Radiometer G 2025C) and a double-junction calomel electrode (Arthur H. Thomas type 4136 B20), the inner tube of which contained saturated KCl and the outer tube

0.5 mol dm^{-3} KNO_3, were inserted and the solution was left to stir for 30 min on a magnetic stirrer with nitrogen gas bubbling through at a steady rate. Then the ester hydronitrate (10 cm^3, 2.000×10^{-2} mol dm^{-3}) was added and the pH of the solution adjusted to the desired value with standard NaOH. The rate of hydrolysis was followed by automatically recording the volume of NaOH delivered per unit time from a syringe burette (Radiometer type SBU11, 2.5-cm^3 capacity) to maintain the set pH value. It was found that the volume of NaOH required to complete the reaction agreed very well with the calculated value. Most reactions were followed to beyond 90% completion with the exceptions of the slower reactions at low pH and low temperature which were followed to *ca.* 80% completion. The difference between the volume of NaOH required to complete the reaction (V_∞) and the volume of NaOH delivery at any time t (V_t) is proportional to the concentration of the unhydrolysed complex. A plot of ln ($V_\infty - V_t$) against t was found to be linear throughout the reaction indicating that the reaction is pseudo-first-order. The rate constant $k_{obs.}$, which can be obtained directly from the slope of the plot, was determined for pH values in the range 5.80—6.80 and at 15, 20, 25, 30, 40, and 45 °C. For each temperature $k_{obs.}$ was plotted against the activities of the hydroxide calculated from the pH value and the ionic product of water, K_w, taken from the literature.[10]

Results and Discussion

(*i*) *Formation Constant.*—The ionisation of the ethyl glycinate hydrochloride or hydronitrate and the reaction of the neutral ester with $[Pd(en)(OH_2)_2]^{2+}$ in solution may be represented by equations (1) and (2) respectively, where $L = H_2NCH_2CO_2C_2H_5$.

$$HL^+ \rightleftharpoons H^+ + L \quad (1)$$

$$[Pd(en)(OH_2)_2]^{2+} + L \rightleftharpoons [Pd(en)L]^{2+} \quad (2)$$

The value of pK_A and log K_1 were evaluated by considering the mass balance and electroneutrality conditions in the solutions. Numerical calculations were done on a UNIVAC-1100 computer. For the calculation of log K_1 only titration points up to 0.5 equivalent of base per ligand were used since beyond this region hydrolysis of the complex becomes quite significant. The values of pK_A and log K_1 at 25 °C and 0.5 mol dm^{-3} KNO_3 are 7.93 ± 0.01 and 7.12 ± 0.03 respectively.

(*ii*) *Hydrolysis.*—The rate of hydrolysis of the complex $[Pd(en)L]^{2+}$ at each temperature and pH may be represented by equation (3), where $k_{obs.}$ is the observed pseudo-first-order

$$-d[complex]/dt = k_{obs.}[complex] \quad (3)$$

rate constant. The values of $k_{obs.}$ were evaluated from the slopes of the linear plots of ln ($V_\infty - V_t$) against time (see Experimental section). The values of $k_{obs.}$ at various pH at 25 °C are shown in Table 1. The values of the $k_{obs.}$ so obtained were then plotted against the hydroxide-ion activities. The plots were found to be linear for all the temperatures studied. Since none of these plots has zero intercept it is clear that the hydroxide ion is not the only attacking nucleophile in the hydrolysis of the complex. The most likely mechanism consistent with the data is that which involves both hydroxide ion as well as a neutral water molecule as a nucleophile according to equations (4) and (5). From (4) and (5) equation (6) is obtained, where

Table 1. Pseudo-first-order rate constants, $k_{obs.}$, for the hydrolysis of $[Pd(en)L]^{2+}$ at 25 °C and 0.5 mol dm^{-3} KNO_3

pH	$10^4 k_{obs.}/s^{-1}$
5.80	2.72
6.00	3.11
6.20	4.06
6.40	4.92
6.60	6.49
6.70	7.51
6.80	8.81

Table 2. Values of rate constants k_1 and k'_2 at 0.5 mol dm^{-3} KNO_3

T/°C	$10^{-4}k_1$/ dm^3 mol^{-1} s^{-1}	$10^4 k'_2/s^{-1}$
15.0	0.80	0.71
20.0	0.93	1.03
25.0	1.06	2.10
30.0	1.18	2.83
35.0	1.43	4.37
40.0	1.48	6.20

$$\text{complex} + OH^- \xrightarrow{k_1} \text{product} \quad (4)$$

$$\text{complex} + H_2O \xrightarrow{k_2} \text{product} \quad (5)$$

$$-d[complex]/dt = k_1[OH^-][complex] + k_2[H_2O][complex] = (k_1[OH^-] + k'_2)[complex] \quad (6)$$

$k'_2 = k_2[H_2O]$, and $k_{obs.} = k_1[OH^-] + k'_2$. Thus k_1 and k'_2 may be obtained as the slopes and intercepts of the linear plots of $k_{obs.}$ against activities of hydroxide. Their values are summarised in Table 2.

The mechanism of the metal-ion promoted hydrolysis of ethyl glycinate has been extensively discussed in the literature. In the case of the inert metal ion Co^{III}, Alexander and Busch [11] were able to show that for $[Co(en)_2L]^{3+}$ the reactive intermediate involves the ester as a chelating ligand co-ordinating to Co^{III} *via* the amino-nitrogen and the carbonyl group. The species where the ester co-ordinates through the amino-group only is relatively inert with respect to hydrolysis.[11] For the more labile metal ions the situation is less clear cut. For example, in the case of Cu^{II}-catalysed hydrolysis of ethyl glycinate, Connor *et al.*[12] proposed an intermediate $[Cu(OH_2)_x(OH)L]^+$ where the ester is again chelated but one of the water molecules occupying the remaining position of Cu^{II} is deprotonated. The species was invoked to explain the non-linear dependence of the rate of hydrolysis on the hydroxide-ion concentration.[12] Conley and Martin [13] showed that the kinetic data may be accounted for by assuming both hydroxide ion as well as neutral water molecules are competing nucleophiles attacking the chelated ester. In this scheme the somewhat unusual intermediate proposed by Connor *et al.* was no longer required. The same mechanism has since been proposed for the Ni^{II}, Zn^{II}, and Co^{II} ethyl glycinate system by Hix and Jones.[14] It is found to be applicable to the $[Pd(en)L]^{2+}$ system discussed here.

In studying labile metal-ion promoted hydrolysis of amino acid esters, one of the principal difficulties encountered is the characterisation of the species actually undergoing hydrolysis. This is particularly difficult when the stability constant of the metal ester complex is relatively low, because the complex may

then constitute only a small fraction of the total ester present. As pointed out by Hay and Morris,[15] kinetic data obtained for metal ester complexes with very high stability constants are much more susceptible to rigorous interpretation. To this end they have studied systems such as cysteine methyl ester, histidine methyl ester and 2,3-diaminopropionic acid methyl ester which form very stable complexes with Cu^{II}, Ni^{II}, and Hg^{II}.[15-17] However, because the ester groups are not directly co-ordinated to the metal ion in the complexes, these systems are essentially different from simple amino acid ester complexes where the ester group is directly co-ordinated.

In $[Pd(en)L]^{2+}$ the value of log K_1 is very large, the complex is almost one thousand times more stable than the simple Cu^{II} complex.[12] This implies that the ester is chelated in the complex. The large stability constant ensures that in the pH range chosen for hydrolysis study practically all the ester present is in the form of the complex with little or no free ester left in solution. Furthermore, since the great majority of Pd^{II} complexes are planar, there is no likelihood of the existence of co-ordinated water molecules on Pd^{II} in $[Pd(en)L]^{2+}$. Thus in this case the species undergoing hydrolysis is well defined. Any possibility of intra- or inter-molecular attack by metal bound hydroxide [18,19] may be ruled out since the trace amount of unco-ordinated $[Pd(en)(OH_2)_2]^{2+}$ will undergo dimerisation at the pH range chosen.[7]

The kinetic data are best interpreted by assuming that both hydroxide ion as well as a water molecule attack the ester group directly co-ordinated to Pd^{II}. The hydroxide ion is a much better nucleophile than the water molecule. However, because of the great difference in concentrations of the two species the contribution of the water hydrolysis pathway becomes appreciable. The value of the base hydrolysis constant K_1 at 25 °C is approximately ten times smaller than the corresponding value for the 1 : 1 copper ethyl glycinate system obtained by Conley and Martin.[13] It is of the same order of magnitude as the values for the Ni^{II}, Zn^{II}, and Co^{II} system.[14] Compared with the rate of hydrolysis of the free ester (0.78 activity^{-1} s^{-1} for neutral ester and 32 activity^{-1} s^{-1} for protonated ester) [13] the rate of hydrolysis of the $[Pd(en)L]^{2+}$ complex is several orders of magnitude larger. However, the increase in the rate of hydrolysis is not as great as might be expected from the large stability constant of the complex. An examination of the available rate constant (k_1) values for various metal-ion ethyl glycinate systems reveals that there is no simple relationship between k_1 and the stability constant of the complexes. A simple relationship might have been expected if the metal ion acts simply as a Lewis acid to withdraw electron density from the reacting centre. The thousandfold increase in the rate of hydrolysis of $[Pd(en)L]^{2+}$ over that of the free ester nevertheless is evidence that the assumption of chelation is justified. For methyl esters of histidine, cysteine, and 2,3-diaminopropionic acid complexes where co-ordination of the ester group to the metal ion has been clearly ruled out the rate increase of the hydrolysis of the complex over the free ester is very much smaller.[15-17]

The energy of activation, E_a, for the base hydrolysis of $[Pd(en)L]^{2+}$ was obtained from the slope of the Arrhenius plot of log k_1 against $1/T$. The other thermodynamic parameters $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ were then evaluated by a standard method.[16] Their values at 25 °C and 0.5 mol dm^{-3} KNO_3 are $\Delta G^{\ddagger} = 11.96$ kcal mol^{-1}, $\Delta H^{\ddagger} = 3.87$ kcal mol^{-1}, $\Delta S^{\ddagger} = -27.1$ cal K^{-1} mol^{-1}, and $E_a = 4.46$ kcal mol^{-1} (1 kcal = 4.184 J). It is interesting to note that the activation energy is significantly less than that for the free ester.[20] It has been found that for the methyl esters of histidine, cysteine, and 2,3-diaminopropionic acid where direct co-ordination of the ester group to metal ions have been ruled out, $\Delta H^{\ddagger}$ values for metal-ion promoted hydrolysis were significantly greater than the corresponding value for the free ester. Thus direct co-ordination of the ester group to metal ion appears to lower the energy of activation for base hydrolysis. This may be one of the main reasons why the rate of hydrolysis of the co-ordinated ester group is so much faster than of the unco-ordinated ester group.

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